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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/851,628	05/06/1997	CHARLES M. COHEN	CIBT-P01-515	6154

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/18/2002

37

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/851,628	COHEN ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,10,12,15-17,24,28,32 and 52-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,10,12,15-17,24,28,32 and 52-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-4,6,10,12,15-17,24,28,32 and 52-55* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 1, 2002 (Paper No. 32) has been entered.

Claims 1-4, 6, 10, 12, 15-17, 24, 28, 32, 52-55 are pending.

Applicant's election with traverse of the species the mature form of OP1, MRI, and chronic diabetic nephropathy in Paper No. 36 is acknowledged. The traversal is on the ground(s) that there would be no additional burden to search all the species. This is not found persuasive because each of the species constitutes a separate search and are patentably distinct unless applicant submits evidence or identifies such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. Manifestation of similar symptoms is not evidence of each of the species being obvious variants. Attorney arguments cannot take the place of evidence.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4, 6, 10, 12, 15-17, 24, 28, 32, 52-55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), to the extent that they are drawn to a nonelected species, there

being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 36.

Claims 1-4, 6, 10, 12, 15-17, 24, 28, 32, 52-55 are being examined to the extent that they read upon the species the mature form of OP1, MRI, and chronic diabetic nephropathy. Any objection and/or rejection of record that is not maintained and/or repeated in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

Maintained Formal Matters, Objections, and/or Rejections:

Double Patenting

Claims 1-4, 6-10, 12, 15-17, 24, 28, 32, 52-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 08643321. It is acknowledged that Applicants will file a terminal disclaimer upon the notification of allowable subject matter.

New formal matters, objections, and/or rejections:

Claim Rejections - 35 USC § 103

Claims 1-4, 6-10, 12, 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6).

Kuberasampath (BB, cited by Applicants) teaches that the body's inflammatory response to tissue injury can cause significant tissue destruction, leading to loss of tissue function. Damage to cells resulting from the effects of inflammatory response has been implicated as the cause of reduced tissue function or loss of tissue function in diseases of the joints (e.g., rheumatoid and osteo-arthritis) and of many organs, including the kidney, pancreas, skin, lung and heart. For example, glomerular nephritis, diabetes, inflammatory bowel disease, vascular diseases such as atherosclerosis and vasculitis and skin diseases such as psoriasis and dermatitis are believed to result in large part from unwanted acute inflammatory reaction and fibrosis. The damaged tissue is often replaced by fibrotic tissue. See paragraph bridging pages 1-2. The immune cell mediated tissue destruction often follows an initial tissue injury or insult; the secondary damage often is the source of significant tissue damage. Humoral agents that mediate tissue damage are produced by adhering neutrophilic leukocytes. See page 2, full paragraph 1. When the interruption of blood flow limits the oxygen supply to the proximal tubular cells of the kidney the cells may become irreversibly injured and the ensuing inflammatory responses to this initial injury provide additional insult to the affected tissue (page 3, full paragraph 1). Where the patient suffers from a chronic inflammatory disease, such as diabetes, the morphogen preferably is administered at regular intervals as a prophylactic (page 13, lines 23-29). OP1 is among the morphogens useful in this invention (page 14, lines 1-3). OP1 comprises the amino acid sequence of SEQ ID NO: 5 (page 15, lines 1-2; page 102, SEQ ID NO: 5), which amino acid

sequence comprises the amino acid sequence of amino acids 330-431 of SEQ ID NO: 1 of the present application. OP1 (page 14, line 30, through page 15, line 17) inhibits the adherence of LTB4 activated PMNs to endothelium (Example 5, pages 74-75), inhibits cellular and humoral inflammatory reactions (Example 7, pages 78-80), and inhibits epithelial cell proliferation (Example 10, page 86-87). Kuberasampath is silent with respect to the administration of OP1 to a mammal afflicted with chronic diabetic nephropathy.

Watanabe (x18) teaches that neutrophilic polymorphonuclear leukocytes are important effector cells in glomerular diseases, including diabetic nephropathy (page 209, column 1, full paragraph 1).

Glassock (v6) teaches that monocytes (macrophages) are present in large numbers in the glomerulus and interstitium in many forms of glomerulonephritis and tubulointerstitial nephritis; interference with the accumulation of these cells within the kidney may ameliorate the clinical and morphological manifestations of the disease (paragraph bridging pages 1294-1295).

Watanabe and Glassock do not teach the administration of OP1 to a mammal afflicted with chronic diabetic nephropathy. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP1 at regular intervals as a prophylactic to a patient suffering from a chronic inflammatory disease, such as diabetes, as taught by Kuberasampath, and to modify that teaching by treating a patient afflicted with chronic diabetic nephropathy, as taught by Watanabe, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to inhibit the adherence of PMNs to endothelium, and thereby limit the progression of diabetic nephropathy and ameliorate the clinical and morphological manifestations of the disease. One of ordinary

skill in the art would have a reasonable expectation that limiting the progression of diabetic nephropathy and ameliorating the clinical and morphological manifestations of the disease would cause a clinically significant improvement in a standard marker of renal function such that the mammal's need for chronic dialysis is delayed or reduced.

The invention is prima facie obvious over the prior art.

Claims 1, 2, 15, 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6) as applied to claims 1, 2 above, and further in view of Coe (z18), Kees-Folts (y18), and Jennerholm (u37).

Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6) as applied to claims 1, 2 above teach administering OP1 to a mammal afflicted with chronic diabetic nephropathy and causing a clinically significant improvement in a standard marker of renal function such that the mammal's need for chronic dialysis is delayed or reduced, as discussed above. Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6) as applied to claims 1, 2 above do not teach examining the mammal by MRI.

Coe (z18) teaches that routine clinical evaluation is often sufficient to suggest that a particular syndrome may be present, but additional laboratory measurements beyond the routine are usually required to establish the diagnosis (page 1251-1252, paragraph bridging left and right columns). Diabetic nephropathy causes chronic renal failure and nephrotic syndrome (Table 233-2). Proof of chronicity is provided by the demonstration of reduction of kidney size by tomography (page 1253, column 2, full paragraph 2).

Kees-Folts teaches that persistent nephrotic syndrome is marked by interstitial fibrosis (page 365, left column, full paragraph 1). Interstitial macrophage infiltration has been identified in diabetic nephropathy (page 366, paragraph bridging columns 1-2). Further, in experimental glomerulonephritides, abrogation of macrophage infiltration results in improved renal function (page 366, column 2, full paragraph 1).

Jennerholm teaches that interstitial fibrosis was correlated to decreases signal intensity on MRI. The correlations found indicate that MRI could contribute to the evaluation of other conditions affecting the kidney (page 503, left column, full paragraph 1).

Coe (z18), Kees-Folts (y18), and Jennerholm (u37) do not teach administering OP1 to a mammal afflicted with chronic diabetic nephropathy and causing a clinically significant improvement in a standard marker of renal function such that the mammal's need for chronic dialysis is delayed or reduced. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP1 to a mammal afflicted with chronic diabetic nephropathy and cause a clinically significant improvement in a standard marker of renal function such that the mammal's need for chronic dialysis is delayed or reduced, as taught by Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6) as applied to claims 1, 2 above, and to modify that teaching by examining the mammal by MRI for an indication of fibrosis, as taught by Jennerholm, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because additional laboratory measurements beyond the routine are usually required to establish the diagnosis of renal syndromes, chronic renal failure and nephrotic syndrome are syndromes associated with diabetic nephropathy, proof of chronicity is provided by the demonstration of reduction of

kidney size by tomography, persistent nephrotic syndrome is marked by interstitial fibrosis, interstitial fibrosis is correlated to decreases signal intensity on MRI, and MRI could contribute to the evaluation of other conditions affecting the kidney.

The invention is prima facie obvious over the prior art.

Claims 1, 2, 17, 24, 28, 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6) as applied to claims 1, 2 above, and further in view of Brenner (u18).

Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6) as applied to claims 1, 2 above teach administering OP1 to a mammal afflicted with chronic diabetic nephropathy and causing a clinically significant improvement in a standard marker of renal function such that the mammal's need for chronic dialysis is delayed or reduced, as discussed above. Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6) as applied to claims 1, 2 above do not teach loss of functional nephron units or reduced GFR.

Brenner teaches the eventual impact of reduction in nephron mass is an alteration in function of virtually every organ system in the body (paragraph bridging pages 1275-1276). In the early stages of CRF, when GFR is reduced to about 35 to 50 percent of normal, overall renal function is sufficient to maintain the patient symptom-free. With further loss of nephron mass the patient develops overt renal failure. See page 1276, left column, full paragraph 1. Conservative therapy is initiated early to control symptoms, minimize complications, prevent long-term sequelae, and slow the progression of renal insufficiency (paragraph bridging pages 1280-1281). Conservative therapy if initiated early (GFR > 40 to 50 mL/min) may retard

progression of renal disease (page 1281, left column, full paragraph 2). Brenner does not teach administering OP1 to a mammal afflicted with chronic diabetic nephropathy and causing a clinically significant improvement in a standard marker of renal function such that the mammal's need for chronic dialysis is delayed or reduced.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP1 to a mammal afflicted with chronic diabetic nephropathy and cause a clinically significant improvement in a standard marker of renal function such that the mammal's need for chronic dialysis is delayed or reduced, as taught by Kuberasampath (BB, cited by Applicants), Watanabe (x18), and Glassock (v6) as applied to claims 1, 2 above, and to modify that teaching by administering OP1 to mammal which ahs a GFR chronically less than about 50% of normal or less than about 40 or 50 mL/min, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to maintain the patient symptom-free, to control symptoms, to minimize complications, to prevent long-term sequelae, to slow the progression of renal insufficiency, and to retard progression of renal disease. The metes and bounds of "50% of a number" are not clearly set forth. With respect to the weight of a male or female, GFR, and nephron mass limitations, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Furthermore, the prior art recognizes the loss of nephron mass as contributing to loss of renal function and recognizes GFR as an indicator of renal function and suggest treatment tied to GFR.

The invention is prima facie obvious over the prior art.

Claim Rejections - 35 USC § 112

Claims 1-4, 6, 10, 12, 15-17, 24, 28, 32, 52-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Support for the limitation "wherein said mammal is not a kidney transplant recipient" cannot be found in the disclosure as originally and its introduction raises the issue of new matter. The specification teaches that subjects that are kidney transplant recipients are subjects in, or at risks of, chronic renal failure (paragraph bridging pages 11-12).

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite over the recitation of "50% of a number" because it is unclear what number is intended. The metes and bounds are not clearly set forth.

Claim Objections

Claims 3, 12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. BMP11 fails to further limit an amino acid sequence having at least 70% amino acid sequence homology with amino acids 30-431 of SEQ ID NO: 1.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

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CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
NOVEMBER 16, 2002